OUTCOME OF MULTI-DRUG RESISTANT TUBERCULOSIS PATIENTS STARTED ON DOTS PLUS (CAT – IV RNTCP REGIMEN) AT GOVERNMENT HOSPITAL OF THORACIC MEDICINE, TAMBARAM SANATORIUM

Dissertation submitted In Partial Fulfilment of the Requirements for the Degree of

DOCTOR OF MEDICINE

PULMONARY MEDICINE

Branch - VII

2009-2012

DEPARTMENT OF PULMONARY MEDICINE
Government Stanley Medical College & Hospital
Chennai-600 001

THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY

CHENNAI-600 032

APRIL 2012

CERTIFICATE

This is to certify that the dissertation on **"OUTCOME OF MULTI-DRUG RESISTANT TUBERCULOSIS PATIENTS STARTED ON DOTS PLUS (CAT – IV RNTCP REGIMEN) AT GOVERNMENT HOSPITAL OF THORACIC MEDICINE, TAMBARAM SANATORIUM"** is a record of research work done by **DR.G.VEL KUMAR** in partial fulfilment for M.D.(PULMONARY MEDICINE) Examination of the Tamilnadu, Dr.M.G.R.Medical University to be held in April 2012.The period of study is from May 2009 to October 2010.

Prof.Dr.C.Chandrasekar, M.D, DTCD,
Head of Department,
Department of Pulmonary Medicine,
Government Stanley Medical College,
Chennai- 600 001.

Prof.Dr.R.Selvi, M.D
Dean i/c,
Govt.Stanley Medical College
and Hospital
Chennai- 600 001.

DECLARATION

I hereby declare that the dissertation entitled **"OUTCOME OF MULTI-DRUG RESISTANT TUBERCULOSIS PATIENTS STARTED ON DOTS PLUS (CAT – IV RNTCP REGIMEN) AT GOVERNMENT HOSPITAL OF THORACIC MEDICINE, TAMBARAM SANATORIUM"** submitted for the Degree of Doctor of Medicine in M.D., Degree Examination, Branch VII, PULMONARY MEDICINE is my original work and the dissertation has not formed the basis for the award of any degree, diploma, associate ship, fellowship or similar other titles. It had not been submitted to any other university or Institution for the award of any degree or diploma.

Place: Chennai Signature of the Scholar

Date :

(Dr.G.VEL KUMAR)

ACKNOWLEDGEMENT

Language with all elaborations seems to be having limitation especially when it comes to expression of feelings. It is incapable of conveying in words all the emotions and feelings one wants to say.

It would take pages to acknowledge everyone who, in one way or another has provided me with assistance, but certain individuals deserve citation for their invaluable help.

I would like to express my heartful thanks to the **Prof.Dr.R.Selvi, M.D,** Dean i/c, Stanley Medical College and Hospital for giving me permission to conduct this study.

I find words insufficient to express my deep sense of gratitude for my esteemed and reverend teacher, my chief **Prof.Dr.C.Chandrasekar M.D, D.T.C.D,** Head of Department, Dept. of Pulmonary Medicine, Stanley Medical College and Superintendent, Govt. Hospital of Thoracic Medicine, Tambaram Sanatorium, for his ever-inspiring guidance and personal supervision. The finest privilege in my professional career has been the opportunity to work under his inspirational guidance.

I thank Associate professor **Dr.O.R.Krishnarajasekhar M.D, D.T.C.D** for his constant encouragement and guidance throughout my postgraduate course.

I am very grateful to Associate professor **Dr.R.Sridhar M.D, D.T.C.D** for providing valuable assistance and timely advice. He has never hesitated in providing support whenever I needed throughout my work.

I would like to express my sincere thanks and heartful gratitude to Associate professor **Dr.A.Mahilmaran M.D, D.T.C.D,** for his constant support, enthusiasm and valuable guidance throughout my work.

Words fall short in expressing my sincere gratitude for other eminent teachers in our department, who helped me in my work; **Dr.N.Ravichandran M.D, Dr.S.Kumar M.D, Dr.Raja M.D.** My work would have been incomplete without their support. I express my sincere thanks to all the assistants in our department for their support.

I have no words to express my sincere and heartful gratitude to my father **Late Shri.V.Gopal** and my mother **Muthulakshmi Gopal** who always supported me throughout my life as a student, guided me to solve my problems and helped me to face all kind of difficulties. Their love, affection and support enabled me to reach this stage of life. This work is dedicated to my beloved father who dedicated his entire life for wellbeing of me and my family. Also, my sincere thanks to my brothers **Dr.Shanmugasundar and Dr.Anandkumar** for their sincere advice and support.

I will always be grateful to my dear wife **Dr.V.Vasuki** for being co-operative, for sharing my enthusiasm and dismay and constantly supporting my

ambitions and struggle. This work would not have been possible without her support in my difficult times.

Last but definitely not the least, I would like to thank all the patients who cooperated with me throughout my work.

Finally it is endowment of spiritualism and rememberance of ALMIGHTY for all that I achieved.

CONTENTS

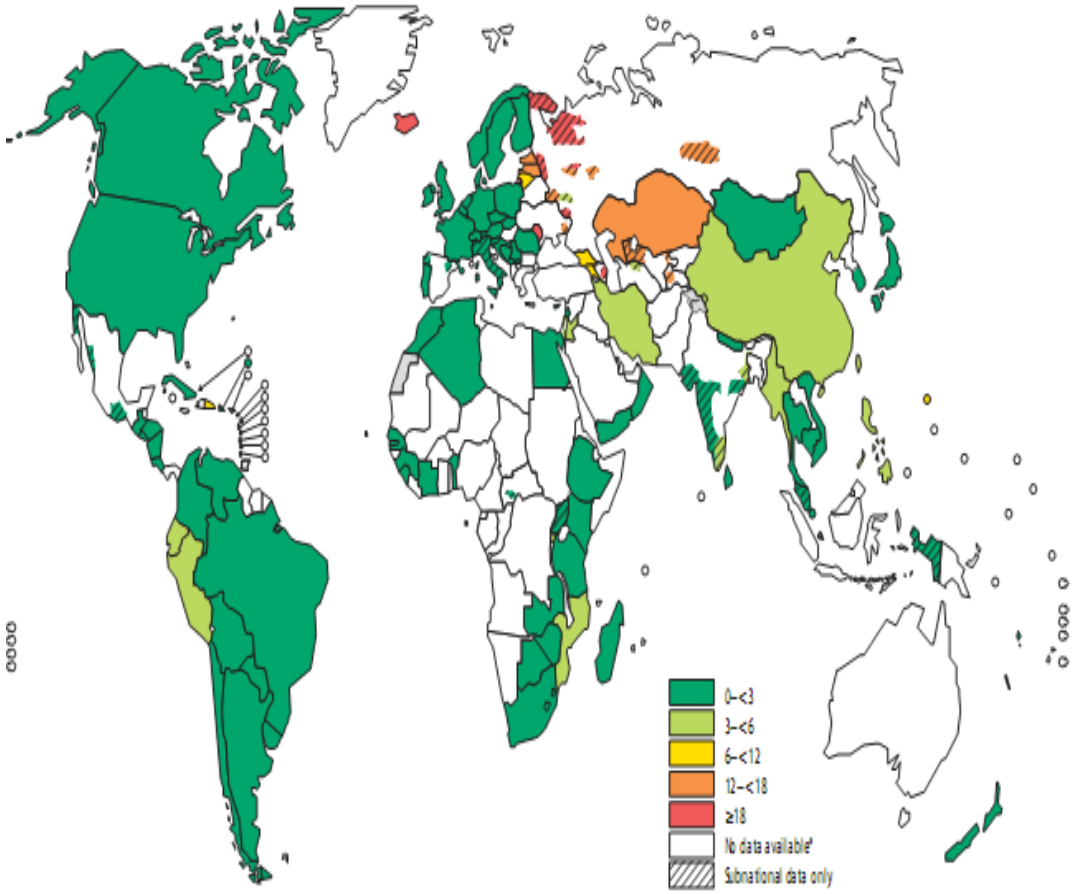
Introduction

INTRODUCTION

The emergence of resistance to drugs used to treat tuberculosis (TB), and particularly Multidrug-resistant TB (MDR-TB), which is defined to resistance to atleast Isoniazid and Rifampicin with or without resistance to other drugs[1], has become a significant health problem in a number of countries and an obstacle to effective TB control[1].

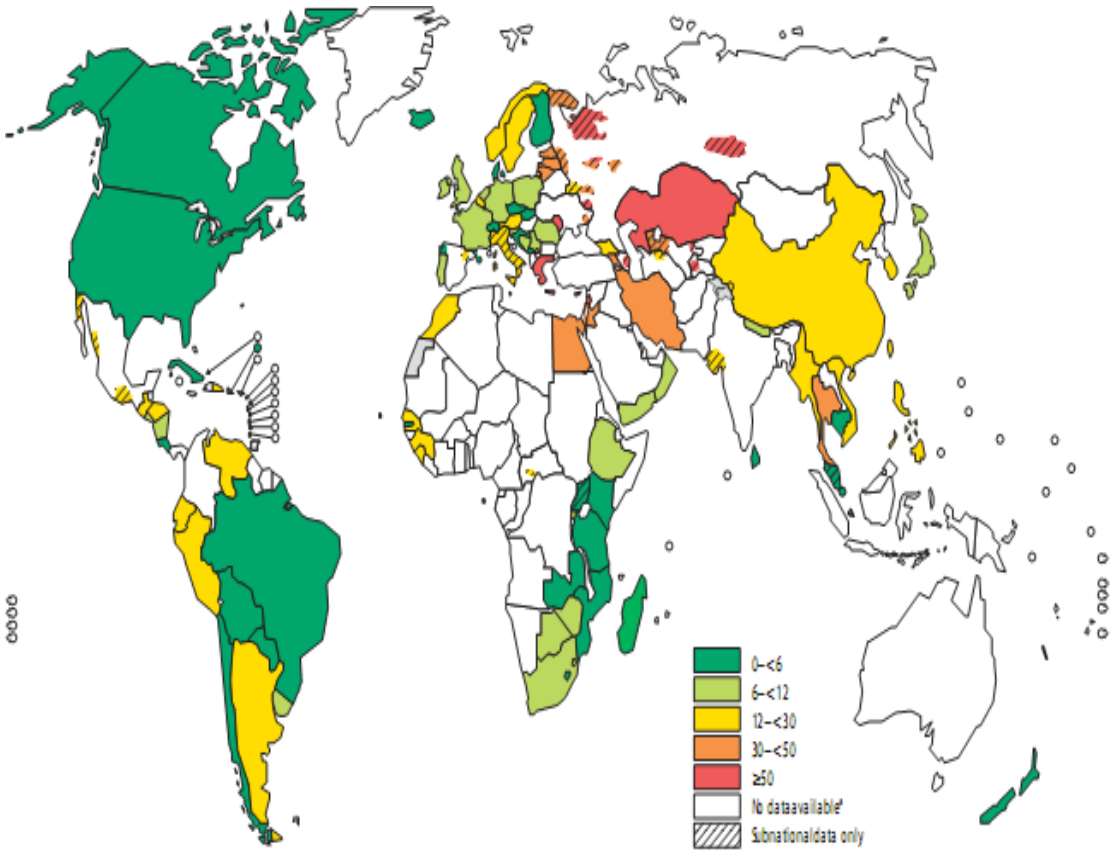
Among all incident TB cases globally, 3.6% (95% CI: 3.0–4.4) are estimated to have MDR-TB[2]. China and India account for almost 50% of the estimated global number of incident MDR-TB cases[2]. High MDR-TB mortality can be addressed through adequate prevention, diagnosis, treatment and care. Since the vast majority of cases are undetected and do not receive adequate care, we expect a global decline in MDR-TB mortality as the coverage and quality of DST and treatment programmes improve globally. Systematic infection control measures have the potential to greatly reduce transmission in hospitals and other congregate settings, and therefore the mortality of, HIV-associated MDR-TB[2].

Distribution of proportion of MDR-TB among new TB cases, 1994–2009[2.]



Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response. WHO/HTM/TB/2010.3

Distribution of proportion of MDR-TB among previously treated TB cases, 1994–2009[2].



Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response. WHO/HTM/TB/2010.3

India is one of the high burden countries for MDR-TB[2].The prevalence of Multi-drug resistant (MDR-TB) are found to be less than 1%-3% in new cases and 12% in re-treatment cases[1, 3, 4]. Specific measures are being taken within the Revised National Tuberculosis Control Programme (RNTCP) to address the MDR-TB problem through appropriate management of patients by implementing a standardized category IV (DOTS PLUS) regimen and strategies to prevent the propagation and dissemination of MDR-TB[1].

Initiation of MDR-TB treatment by DOTS PLUS therapy was started at Ahmedabad, Gujarat in August 2007[5].subsequently it was started in other districts of India in a phased manner. The programme was started at January 2009 in Tamilnadu. The only functional DOTS PLUS site in Tamilnadu is Government Hospital Of Thoracic Medicine, Tambaram Sanatorium[5].

GHTM, TAMBARAM SANATORIUM

DOTS PLUS WARD

GTHM, TAMBARAM SANATORIUM

While MDR-TB control in 2010 was estimated to re-quire less than 20% of all TB control programme budgeted costs globally in 2009, by 2015 this proportion is expected to reach 50%[2]. In five of these countries (the Democratic Republic of the Congo, India, Nigeria, Pakistan and Uzbekistan), more than two-thirds of the planned budget represents a funding gap[2].

Since treatment of MDR-TB is very critical in preventing the spread of resistant strains in the community and to reduce the emergence of XDR-TB which is a extremely fatal disease and in helping to reduce the economic burden to the developing country like India in an indirect way, our aim was to study the outcome of 100 MDR-TB patients one year after starting DOTS

PLUS therapy who are enrolled from May 2009 to May 2010 at GHTM, Tambaram Sanatorium.

This will give an interim outcome and effectiveness of DOTS PLUS programme in Tamilnadu. The profile of patients entering DOTS PLUS programme in Tamilnadu are also studied.The complexity of disease and treatment and development of XDR-TB among treatment failures are important issues to be addressed and should be carefully followed up.

Review of Literature

REVIEW OF LITERATURE

Multidrug resistant tuberculosis:

MDR-TB is defined as resistance to Isoniazid and Rifampicin, with or without resistance to other anti-TB drugs[1].

Causes of drug resistant tuberculosis:

Drug-resistant TB has microbial, clinical, and programmatic causes. From a microbiological perspective, the resistance is caused by a genetic mutation that makes a drug ineffective against the mutant bacilli. An inadequate or poorly administered treatment regimen allows drug-resistant mutants to become the dominant strain in a patient infected with TB. However it should be stressed that MDR-TB is a man-made phenomenon – poor treatment, poor drugs and poor adherence lead to the development of MDR-TB[1].

Magnitude of MDR-TB problem in India:

The prevalence of multi-drug resistant TB (MDR-TB) is less than 1% to 3% in new cases and around 12% in re-treatment cases[1, 3, 4].

A retrospective analysis of various randomized clinical trials conducted by the TRC with various Rifampicin containing regimens in the initial intensive phase, and with and without Rifampicin in the continuation phase,

revealed an overall emergence of resistance to Rifampicin in only 2% of patients, Despite a high level (18%) of initial resistance to isoniazid, either alone or in combination with other anti-TB Drugs[1, 6].

Case definitions:

MDR-TB Suspect[1]:

- Any TB patient who fails an RNTCP Category I or III treatment regimen;
- Any RNTCP Category II patient who is sputum smear positive at the end of the fourth month of treatment or later; or
- Close contacts of MDR-TB patients who are found to have smear positive pulmonary TB (PTB) disease

Confirmed MDR-TB case[1]:

An MDR-TB suspect who is sputum culture positive and whose TB is due to Mycobacterium tuberculosis that are resistant in-vitro to at least Isoniazid and Rifampicin (The culture and DST result being from an RNTCP accredited laboratory). Patients with are not MDR but have any Rifampicin resistance will also be treated with Cat IV regimen.

Diagnostic examination[1]

Presently conventional solid egg-based Lowenstein-Jensen (LJ) media will be used for primary culture at the RNTCP accredited laboratory. DST will be performed for streptomycin (S), isoniazid (H),rifampicin (R) and ethambutol (E) only.

Multi-drug resistant tuberculosis and DOTS-Plus[1]**:**

RNTCP has started Standardised Treatment Regimen (Cat IV-DOTS PLUS REGIMEN) for the treatment of MDR-TB cases (and those with Rifampicin resistance) under the programme. Cat IV regimen comprises of 6 drugs- kanamycin, levofloxacin, ethionamide, pyrazinamide, ethambutol and cycloserine during 6-9 months of the Intensive Phase and 4 drugs- ofloxacin (levofloxacin), ethionamide, ethambutol and cycloserine during the 18 months of the Continuation Phase. p-aminosalicylic acid (PAS) is included in the regimen as a substitute drug if any bactericidal drug (K, Ofl, Z and Eto) or 2 bacteriostatic (E and Cs) drugs are not tolerated.

RNTCP CATEGORY IV REGIMEN: 6 (9) Km Ofx (Lvx) Eto Cs Z E / 18 Ofx (Lvx) Eto Cs E.

Dosage and weight band recommendations[1]:

S.NO	Drugs	16-25 Kgs	26-45 Kgs	>45 Kgs
1	KANAMYCIN	500 mg	500 mg	500 mg
2	LEVOFLOXACIN	200 mg	500 mg	750 mg
3	ETHIONAMIDE	375 mg	500 mg	750 mg
4	ETHAMBUTOL	400 mg	800 mg	1000 mg
5	PYRAZINAMIDE	500 mg	1250 mg	1500 mg
6	CYCLOSERINE	250 mg	500 mg	750 mg
7	PAS	5 gm	10 gm	12 gm
8	PYRIDOXINE	50 mg	100 mg	100 mg

Treatment Outcomes[1]

Cure: An MDR-TB patient who has completed treatment and has been consistently culture negative (with at least 5 consecutive negative results in the last 12 to 15 months). If one follow-up positive culture is reported during the last three quarters, patient will still be considered cured provided this positive culture is followed by at least 3 consecutive negative cultures, taken at least 30 days apart, provided that there is clinical evidence of improvement.

Treatment completed: An MDR-TB patient who has completed treatment according to guidelines but does not meet the definition for cure or treatment failure due to lack of bacteriological results.

Death: An MDR-TB patient who dies for any reason during the course of MDR-TB treatment

Treatment failure: Treatment will be considered to have failed if two or more of the five cultures recorded in the final 12-15 months are positive, or if any of the final three cultures are positive.

Treatment default: An MDR-TB patient whose MDR-TB treatment was interrupted for two or more consecutive months for any reasons.

Transfer out: An MDR-TB patient who has been transferred to another reporting unit (DOTS Plus site in this case) and for whom the treatment outcome is not known.

Treatment stopped due to adverse drug reactions: A patient on MDR-TB treatment who develops severe adverse reactions and could not continue the MDR-TB treatment in spite of the management of the adverse reactions as per the defined protocols and decision has been taken by the DOTS-Plus site committee to stop treatment

Treatment stopped due to other reasons: A patient on MDR-TB treatment who could not continue the MDR-TB treatment for any other medical reason (than adverse drug reactions), and a decision has been taken by the DOTS-Plus site committee to stop treatment.

Switched to Category V treatment: A Category IV patient who during treatment is identified as an "XDR-TB suspect" and who is found to have XDR-TB on testing by an NRL, who subsequently has had their Category IV treatment stopped and RNTCP Category V treatment initiated.

Still on treatment: An MDR-TB patient who, for any reason, is still receiving their RNTCP CAT IV treatment at the time of the submission of the RNTCP DOTS- Plus Treatment Outcome Report.

DOTS PLUS treatment in Tamilnadu:

DOTS PLUS treatment was started in India at Ahmedabad, Gujarat at August 2007[5].susequently it was introduced in other states of India in a phased manner. The programme was started in Tamilnadu from January 2009 with Government Hospital Of Thoracic Medicine, Tambaram Sanatorium being the only functional DOTS PLUS site. In Tamilnadu it was started initially only in 4 districts. Gradually further districts were included in the programme and by 2011 all districts were covered in Tamilnadu.

Accredited laboratory in Tamilnadu[5]:

- IRL at Chennai has been accredited for Solid C & DST in January 2009.
- CMC, Vellore laboratory has been accredited in January 2009.

Literature review shows that:

In a literature, Clin Infect Dis. (2008) 47 (4): 496-502[7]: Assessment of treatment outcomes revealed that 86 patients (55%) were cured, 16 (10%) completed therapy, 10 (6%) died, 15 (10%) defaulted treatment, 22 (14%) experienced treatment failure, and 6 (4%) were transferred to another medical center. In total, 102 patients (66%) had favourable outcomes, and 53 (34%) had unfavourable outcomes. According to this study favourable outcome was about 66%.But limitation in this study is that it does not show the co morbid factors and the factors that are associated with unfavourable outcomes.

Leimane V et al [8] observed that, 135 (66%) patients were cured or completed therapy, 14 (7%) died, 26 (13%) defaulted, and treatment failed in 29 (14%). Of the 178 adherent patients, 135 (76%) achieved cure or treatment completion. This study has shown good cure rate, low death rate.

Shean KP et al[9] observed that (49%) were cured or completed treatment, 68 (14%) died, 144 (29%) defaulted from treatment, 27 (5%) failed, 10 (2%) transferred out and 3 (<1%) remained on treatment. Among 410 patients who had not transferred out or died, 281 (69%) had 2-year data available: 185 (66%) were cured or completed treatment, 32 (11%) were retreated for TB and 64 (23%) died. This study review shows that defaulter rate (29%) has been quiet high, but failure rate is very low (5%).

V.K. Arora et al [10] observed that, off 66 patients included for analysis, 53 (80.9%) became culture-negative, 77.3% of these within three months. Four (6.1%) failed to convert within nine months. Rest died or defaulted. Among 28 patients completing two years of treatment, 67.9% were cured, 14.3% died, 17.9% defaulted, but none failed treatment. Cycloserine had to be stopped in five patients, and kanamycin in three patients due to adverse effects. This review mentions about the drug toxicity profile and also defaulter rate was quiet high (17.9%).

WHO report on Global outcome of MDR-TB, 2010[2]:

In total, outcomes were reported for 1589 new cases and for 2911 previously treated cases. These outcomes represent 8% of new and 14% of previously treated MDR-TB cases expected to have occurred among the TB cases notified by these countries in the same year[2]. Overall treatment success was 60% (95%CI: 55–66) after adjustment for clustering at country level. Among new cases, treatment success averaged to 64% (95%CI: 55–72), and 8% died (95%CI: 5–11). Treatment success for previously treated cases was 58% (95%CI: 52–64) and 13% died (95%CI: 10–15)[2].

This global report on MDR-TB outcome shows that worldwide the cure rate is 61%(after adjusting for clustering by country)[2].Death rate is quiet low (8%) in new MDR-TB cases compared to previously treated cases where death rate is 13%[2].

Marie flament-saillour et al[11] observed that, among 51, Patients were primarily men (74.5%) with a median age of 45 yr (range, 20 to 78 yr). Thirty-two (62.7%) were foreign born, 21 (41.2%) had a low socioeconomic status, 19 (37.3%) had no stable housing, and eight (15.7%) were HIV-co infected. The median duration of survival of MDR-TB cases was 30.7 mo (CI_{95}, 25.2 to 36.1). There was an excess mortality among patients with MDR-TB compared with patients with drug-susceptible tuberculosis (Logrank test = 15.45, $p < 0.001$). MDR-TB case-patients co infected with HIV had a shorter

duration of survival (median, 2.1 mo; CI_{95}, 0.9 to 3.3) than did drug-susceptible HIV-co infected control-patients (median > 36 mo).

This study analyzed the socioeconomic status, HIV coinfection and showed that MDR-TB co infected with HIV had higher mortality compared to non HIV with MDR-TB.

Orenstein EW et al[12] observed that Individualised treatment regimens had higher treatment success (64%, 95% CI 59-68%) than standardised regimens (54%, 95% CI 43-68%), although the difference was not significant.

We according to the programme are following standardised treatment regime for treatment of MDR-TB based on weight of the individual. Various studies have been done to assess the efficacy of standardised and individual regimen. But the study did not show any significant difference in the outcome.

Holtz TH et al[13] observed that, Mortality among MDR-TB defaulters was high. Interventions to reduce default from MDR-TB treatment should center on substance abuse treatment, patient education and support and improving provider-patient relationships. This study assessed the cause for mortality among MDR-TB patients and concluded that substance abuse treatment and health education is very much essential to create awareness and prevent the spread of disease and also to reduce defaulters and thereby reducing mortality due to the disease.

So it is important to follow up the patients with MDR-TB and also to analyse the socio-economic and co morbid factors to know about the course of the disease, adverse effects of drugs, since it is very much essential to arrest the spread of resistant strains and to reduce the emergence of XDR-TB and help to decrease economic burden to the country in an indirect way.

Aim of the Study

AIM OF THE STUDY

1) To study the outcome of Multidrug-resistant tuberculosis (MDR-TB), patients 1 year after starting on DOTS PLUS (CAT IV RNTCP) enrolled from May 2009 to May 2010 at Government Hospital of Thoracic Medicine, Tambaram Sanatorium.

2) To analyze the factors associated with death and culture positivity at the end of one year.

Materials & Methods

MATERIALS AND METHODS

STUDY DESIGN

Prospective study

INCLUSION CRITERIA:

Culture proved 100 MDR-TB patients who were enrolled from May 2009 to May 2010 and initiated on DOTS PLUS therapy at GHTM is followed up for the period of one year.

EXCLUSION CRITERIA:

1) Patients who are under 15 years of age

2) History of more than 1 month treatment with any second line anti-TB drug.

METHOD:

Data's were recorded from TB.HIV.Information.System (t.h.i.s).Follow up of patients were based on RNTCP DOTS PLUS guidelines. The clinical and microbiological outcome at the end of one year and factors associated with death and culture positivity were analyzed using multi variate analysis.

FOLLOW UP – AS PER DOTS PLUS GUIDELINES[1]:

The follow up of MDR-TB patients started on DOTS PLUS (CAT IV REGIMEN) will be mainly based on both microbiological and clinical criteria. The follow up will be done as per RNTCP DOTS PLUS guidelines.

1. **Smear and culture examination**:

Four sputum specimens will be collected and examined by smear and culture at least 30 days apart from the 3rd to 7th month of treatment (i.e. at the end of 3, 4, 5, 6, 7 months) and at 3 monthly intervals from the 9th month onwards till the completion of treatment (i.e. at the end of 9, 12, 15, 18, 21, 24). The sputum for AFB smear will be collected and examined at respective DMC/DTC. The sputum for AFB culture will be collected and transported in CPC bottles from the respective DTC to the RNTCP accredited laboratory[1].

The importance of the sputum examination during treatment needs to be emphasized, since the most important objective evidence of improvement is the conversion of sputum smear and culture to negative. Patients will be considered culture converted after having two consecutive negative cultures taken at least one month apart. Time to culture conversion is calculated as the interval between the date of MDR-TB treatment initiation and the date of the first of these two negative consecutive cultures (the date that the sputum specimens are collected for culture should be used). Similarly patients will be considered smear converted after having two consecutive negative smears taken at least

one month apart. Two separate indicators, one based on sputum smears and the other on cultures will be calculated and interim reports will be given by the state level DOTS Plus site for smear and culture after completing 6 months and 12 months of treatment. Though smear conversion can be taken as an indicator, culture conversion which reflects viability of tubercle bacilli, is more sensitive and is necessary to monitor progress in MDR-TB patients. Good quality sputum is essential to get proper results[1].

2. Clinical monitoring:

Every month during intensive phase and 3 monthly once during continuation phase by the DTO and if patient fell ill during the course of treatment it will be intimated to dots plus site and if necessary patient will be admitted.

1. Weight of the patient during every visit.
2. Serum Creatinine: Every month for first three months and then every 3 months till patient is receiving kanamycin.
3. Chest X-ray: During end of Intensive phase and end of treatment and when clinically indicated.
4. Looking for any adverse effects due to drugs.

Socio-demographic and co morbid factors:

Further, Socio-demographic Profile of patients entering into DOTS PLUS treatment in Tamilnadu from May 2009 to May 2010 and also the co morbid factors associated with death, culture positivity at the end of one year were analyzed using multivariate analysis.

ETHICAL JUSTIFICATION

The various investigations and procedures that will be used in this study will be as per RNTCP guidelines. The identity of each patient will be kept confidential. This study will not violate medical ethics in anyway and it will help to know the outcome of MDR-TB treatment in Tamilnadu.

Observation & Results

OBSERVATIONAND RESULTS

The study on the OUTCOME OF MULTIDRUG RESISTANT TUBERCULOSIS PATIENTS STARTED ON DOTS PLUS (CAT-IV RNTCP REGIMEN) AT GOVERNMENT HOSPITAL OF THORACIC MEDICINE, TAMBARAM SANATORIUM between May 2009 to May 2010 and the following observation were made.

OUTCOME AT THE END OF 1 YEAR:

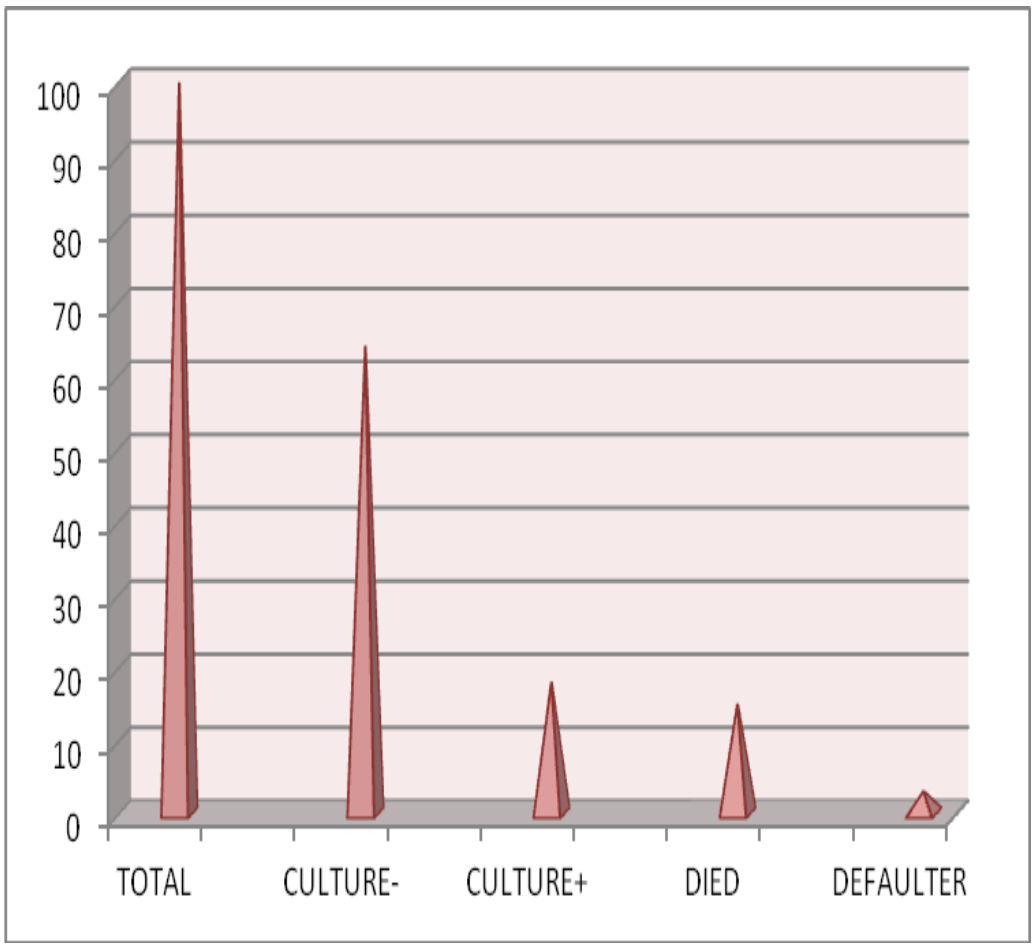
- Off the 100 patients analysed in our study who were started on treatment, 64% remained culture negative at the end of 1 year,15% died ,3% defaulted and 18% remain culture positive at the end of 1 year.

ONE YEAR OUTCOME OF MDR-TB PATIENS: TABLE -1

TOTAL NUMBER OF MDR-TB PATIENTS	100
CULTURE NEGATIVE AT THE END OF ONE YEAR	64
CULTURE POSITIVE AT THE END OF ONE YEAR	18
NUMBER OF PATIENTS DIED WITHIN ONE YEAR	15
DEFAULTERS WITHIN ONE YEAR	3

ONE YEAR OUTCOME OF MDR-TB PATIENTS

CHART-1



- Off the 64 culture converted patients, 40 patients converted in 3months after initiation of treatment.4 patients in 4 months, 6 patients in 5 monts,8 patients in 6 months,2 patients in 7 months,2 patients in 9 months and 2 patients in 12 months.

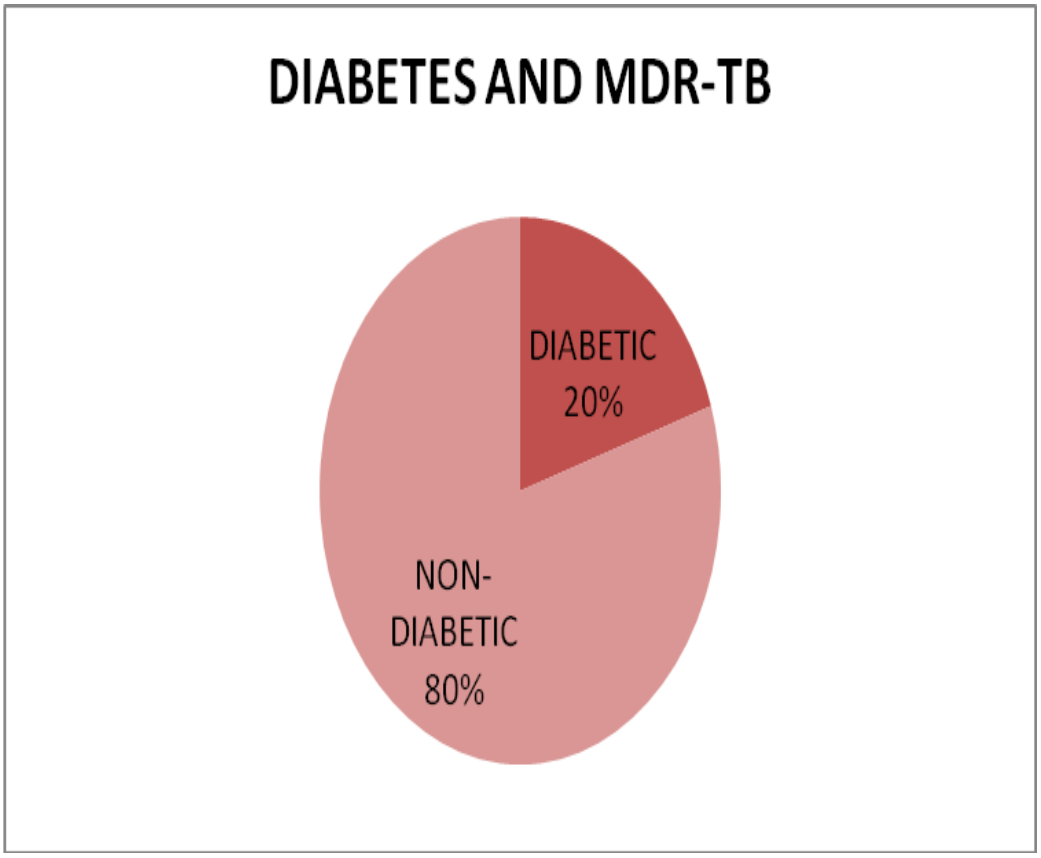
CULTURE CONVERTED PATIENTS WITHIN ONE YEAR = 64

TABLE – 2

No. of patients Culture converted in 3 months	40 (62.5%)
4 months	4 (6.25%)
5 months	6(9.37%)
6 months	8(12.5%)
7 months	2(3.12%)
9 months	2(3.12%)
12 months	2(3.12%)

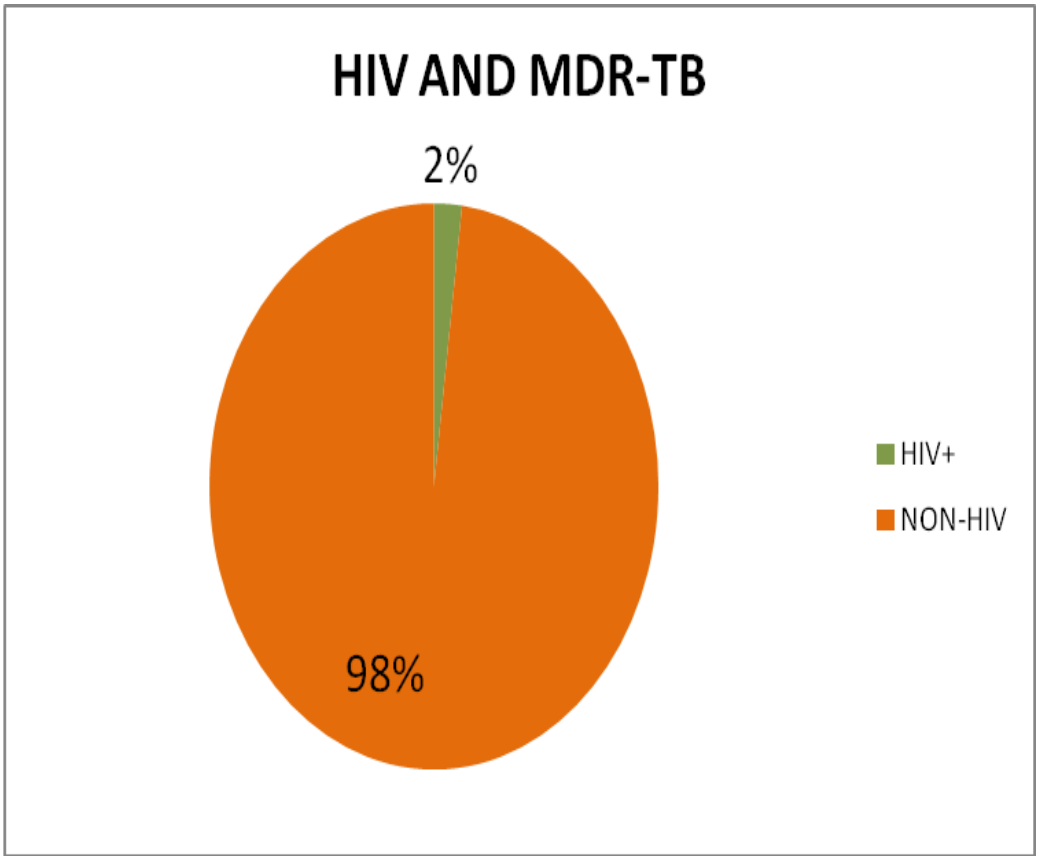
- In our study among 100 MDR-TB patients, 20 were diabetics who were started on DOTS PLUS treatment.

CHART-2



Among 100 MDR-TB patients, HIV coinfection was present in only 2 patients in our study.

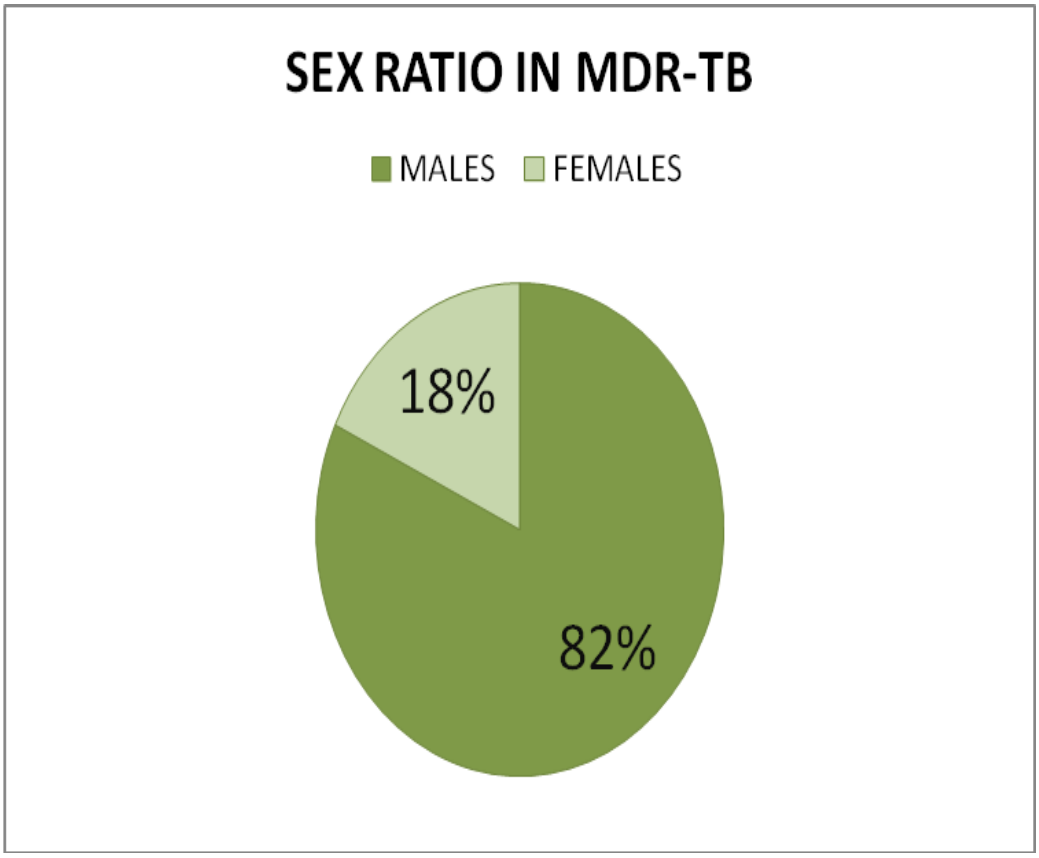
CHART-3



- **<u>Socio-demographic profile of 100 patients</u>**:

Among 100 patients, 82 patients were male, remaining 18 were females in our study.

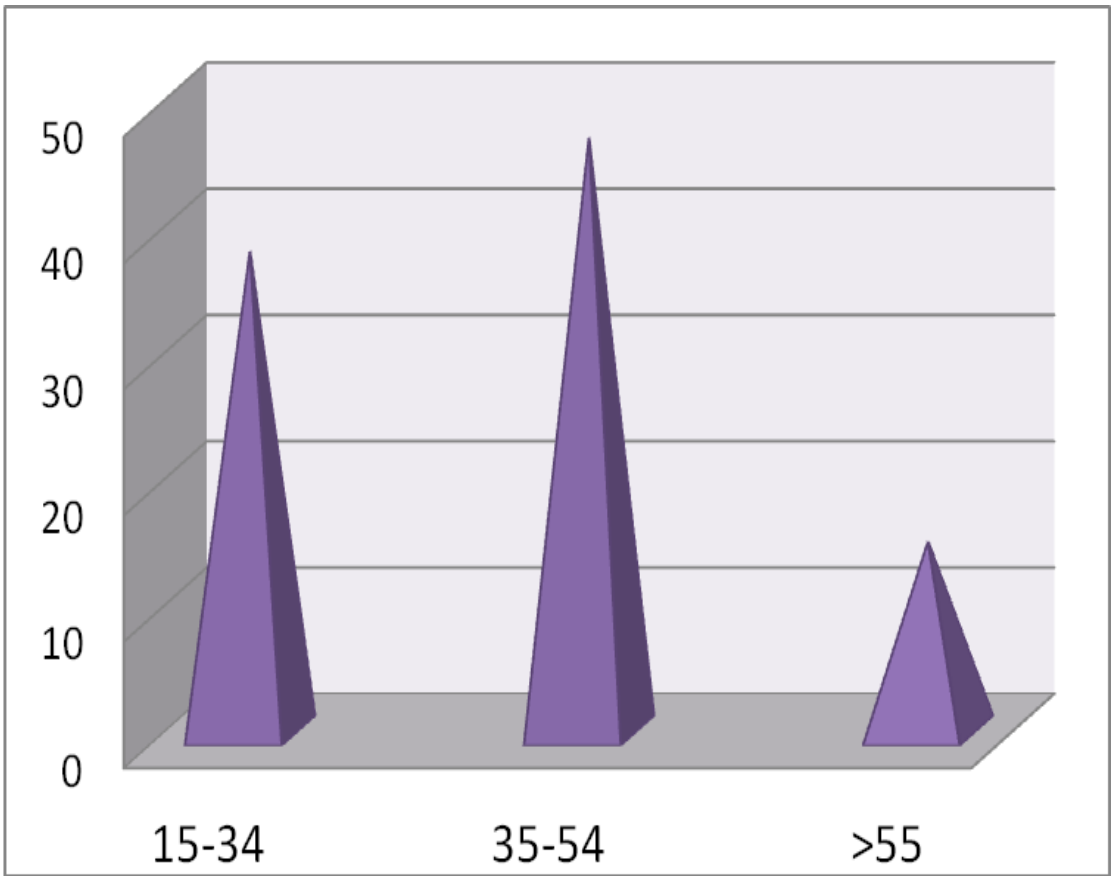
CHART-4



- Off the 100 patients, 38 patients were in the age group of 15 – 34 years, 47 patients were in 35-54 years group, 15 patients were above 55 years of age.

AGE WISE INCIDENCE OF MDR-TB

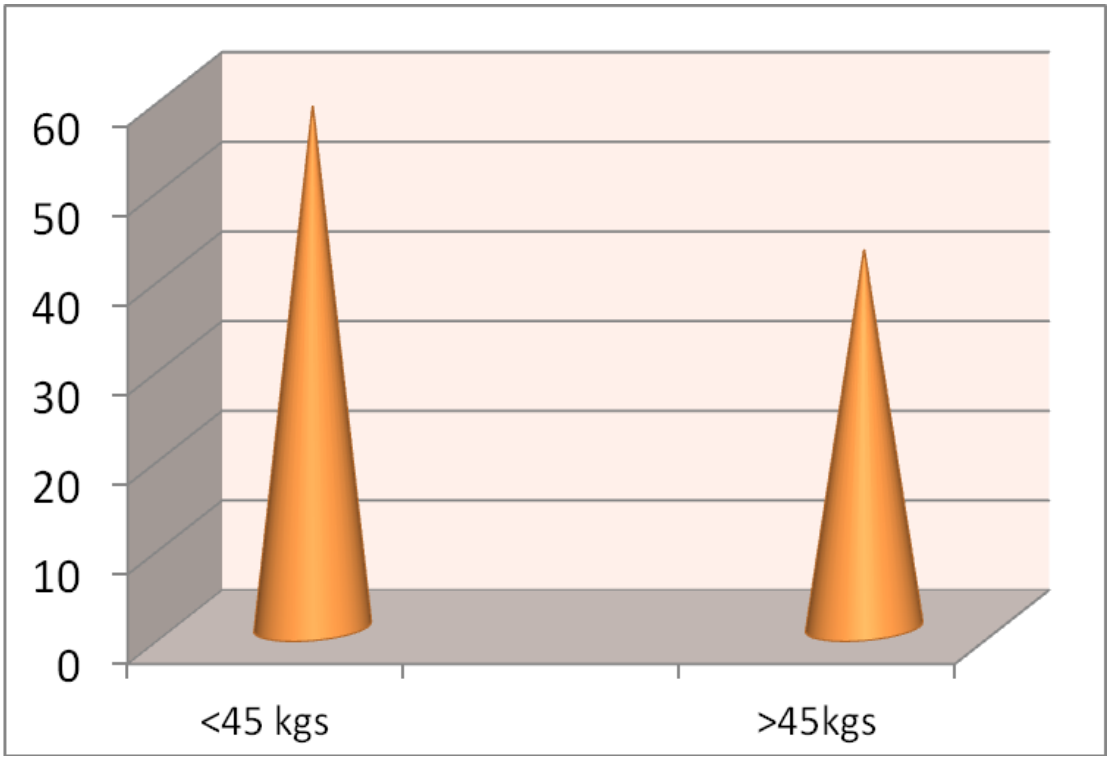
CHART-5



- Off the 100 patients, 58 patients belongs to <45 kg weight band, 42 patients belongs to >45 kg weight band in our study group.

PRE-TREATMENT WEIGHT AMONG 100 MDR-TB PATIENTS

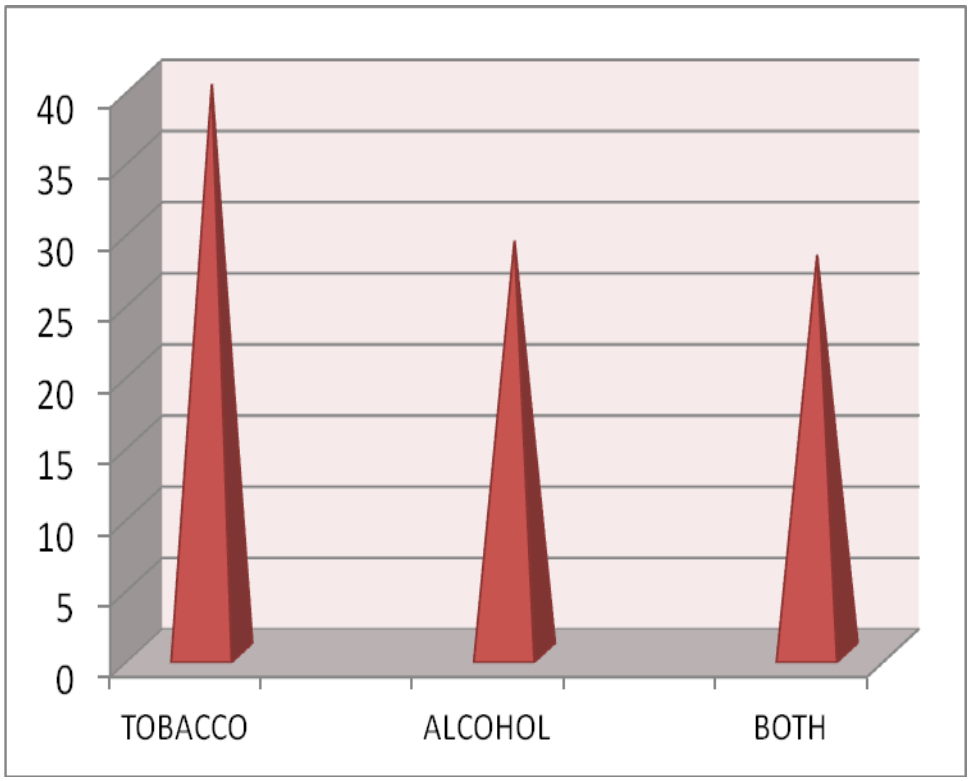
CHART-6



- Off the 100 patients, 40 were tobacco users and 29 were alcoholic and 28 were both in our study group.

TOBACCO AND ALCOHOL USE AMONG MDR-TB PATIENTS

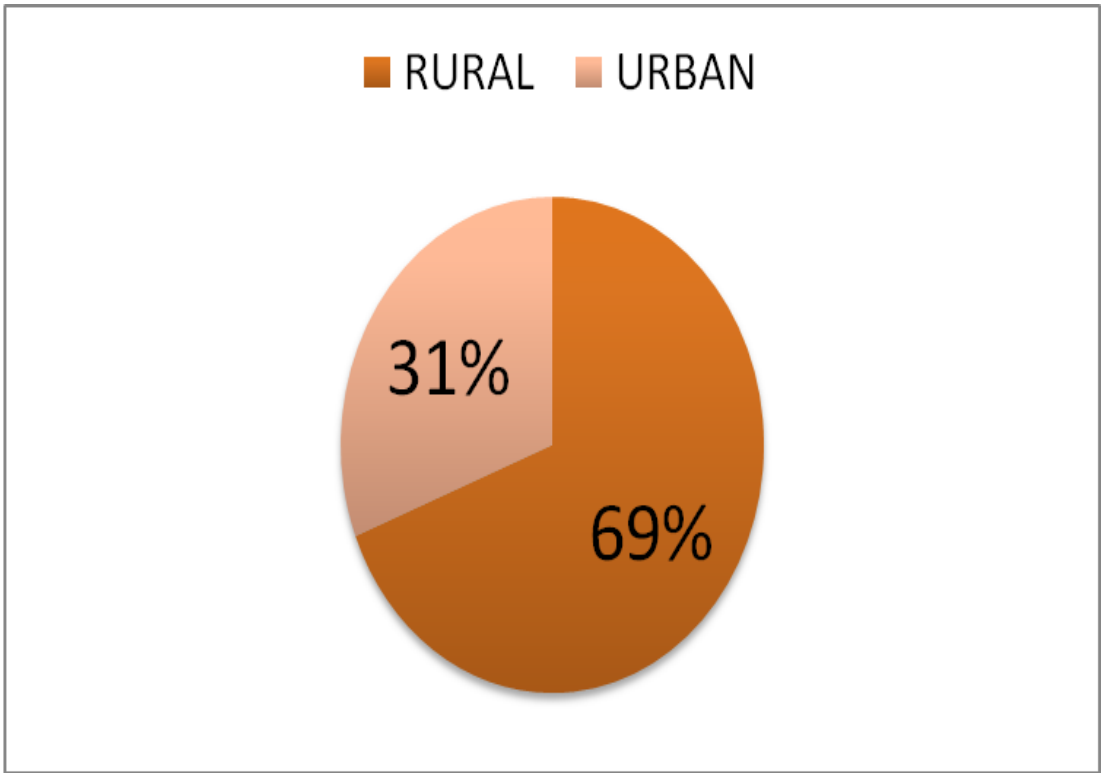
CHART-7



- In our study group of 100 patients, 69 patients were from rural area and 31 from urban area.

RESIDENTIAL STATUS OF MDR-TB PATIENTS

CHART-8



- **<u>Further factors associated with death and culture positivity were analyzed</u>**:

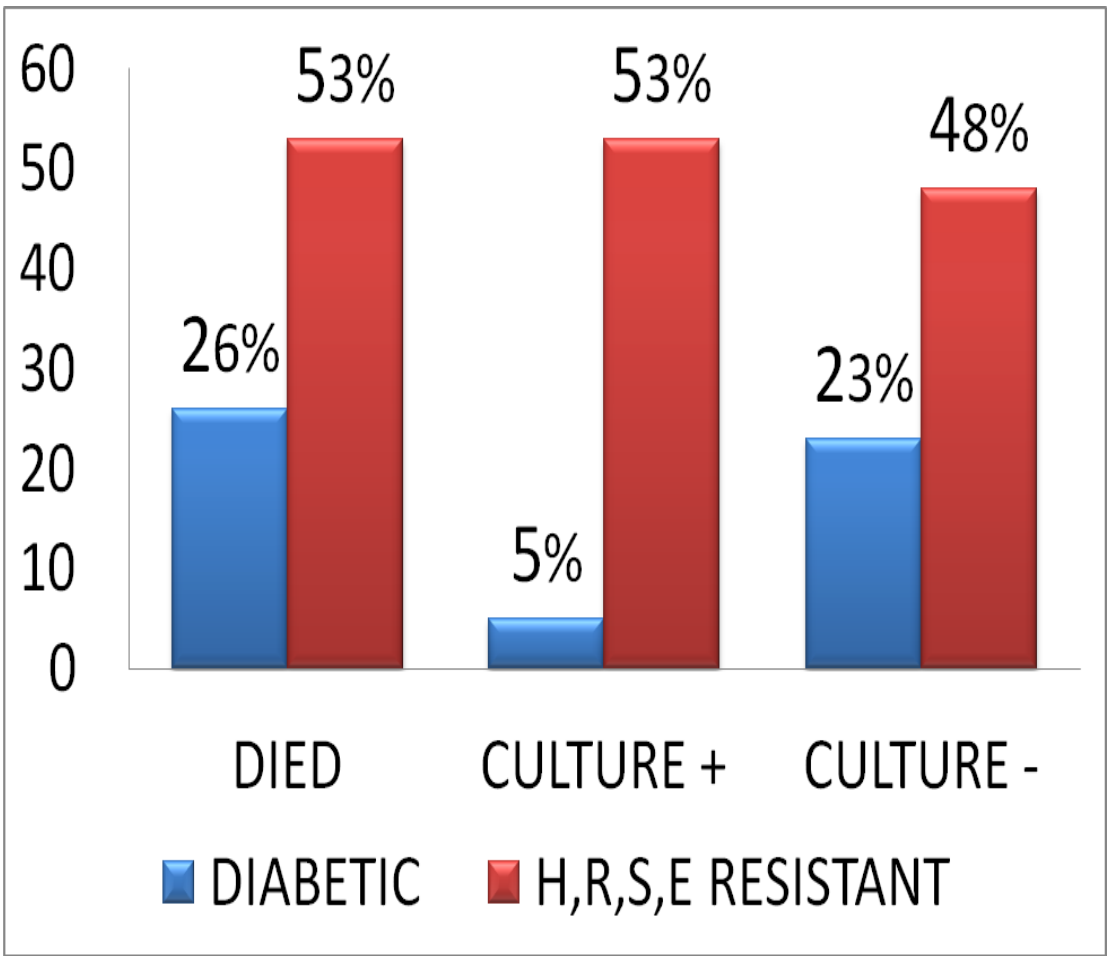
- Out of 15 who died 26% (4 patients) were diabetics and 53 % (8 patients) were resistant to (H, R, S, and E). Among the culture positives 5% (1 patient) were diabetic, 53% (10 patients) were resistant to (H, R, S, and E).Among culture negative patients at 1 year, 23 %(15 patients) were diabetic and 48% (31 patients)were (H,R,S,E) resistant.

TABLE -3

CHARACTERISTICS	**DIED** **TOTAL=15**	**CULTURE POSITIVE PATIENTS** **TOTAL=18**	**CULTURE NEGATIVE PATIENTS** **TOTAL=64**
DIABETES	4(26%)	1(5%)	15(23%)
H,R,S,E RESISTANCE	8(53%)	10(53%)	31(48%)

DIABETES AND HRSE RESISTANCE AMONG 3 GROUPS

CHART-9



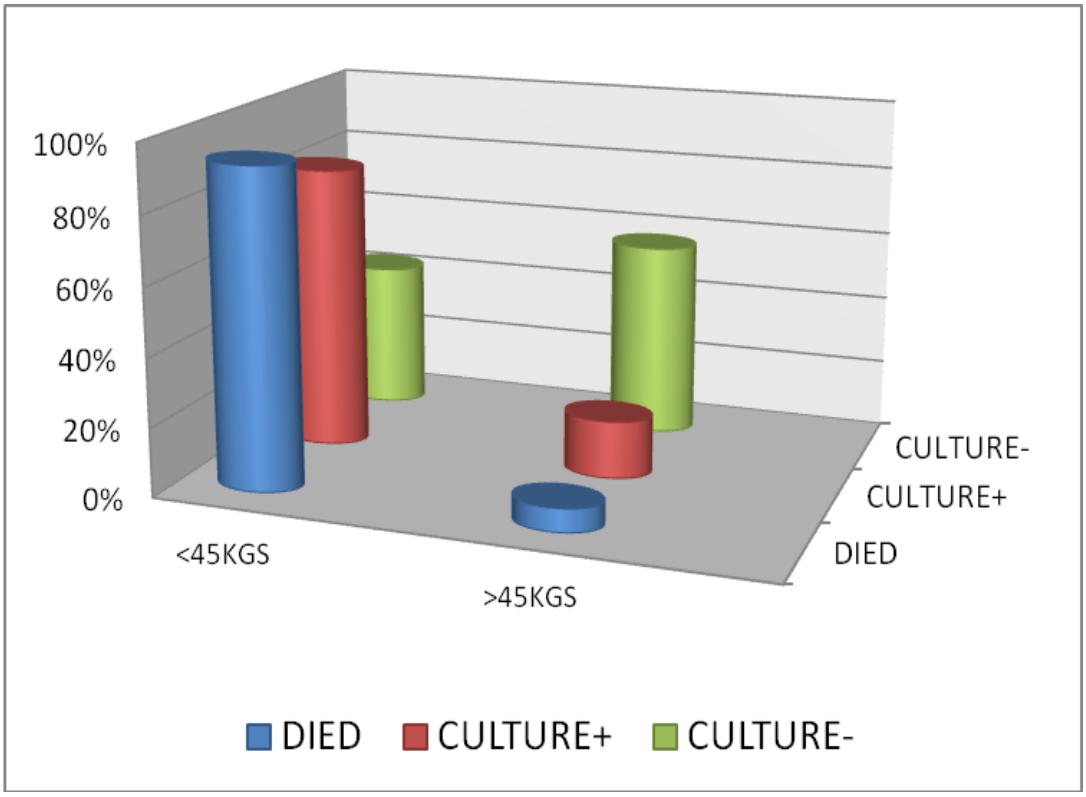
- Among 15 patients who died, 14 patients (93%) were in the <45kg weight band. Among 18 culture positive patients at the end of 1 year, 15 were (83%) in the <45 weight band. Only 43% were in <45 kg weight band among culture negative patients.

TABLE - 4

CHARACTERISTICS	**DIED** **N=15**	**CULTURE POSITIVE** **N=18**	**CULTURE NEGATIVE** **N=64**
WEIGHT < 45 KGS	14(93%)	15(83%)	28(43%)

PREVALANCE OF WEIGHT AMONG 3 GROUPS

CHART – 10



Discussion

DISCUSSION

This study based on 100 patients in Tamilnadu who were started on standardized DOTS PLUS regimen recommended by RNTCP for the treatment of MDR-TB appears to be effective in terms of high culture conversion rate (64%),low defaulter rate(3%) at the end of 1 year. Death rate is 15%.Further, 18% of patients remain culture positive at the end of 1 year (TABLE & CHART-1).

Study done by V.K Arora et al observed that MDR-TB patients achieved good results with a sputum culture conversion rate of 80.9% and cure rate of 67.9% with no failures[10]. Pauline Joseph et al observed that standardized regimen recommended by RNTCP for the treatment of MDR-TB cases in India appears to be effective in terms of high culture conversion, high cure (66%) and low death (8%)[14.]

Other studies conducted across the country showed similar results. Singla et al observed 61% cure rate in a study conducted at New Delhi[15.] Malla et al also observed 70% cure rate in a study conducted at Nepal[16.]

In contrast, Suarez PG et al observed only 48 per cent favourable response in Peru using a standardized regimen for chronic TB patients with MDR-TB[17].

Global report on MDR-TB outcome shows that worldwide the cure rate is 61 %(after adjusting for clustering by country)[2].Our results showed 64% culture conversion rate at the end of 1 year using standardized DOTS PLUS regimen as per RNTCP guidelines.

In our study among 64 culture converted patients, 40 (62.5%) patients achieved culture conversion at the end of 3 months.4 (6.25%) patients in 4 months,6(9.37%) patients in 5 months,8(12.5%) patients in 6 months and 2 (3.12%) patients in 7,9 and 12 months. This shows that most of the culture conversion occurs in 3 months after initiating treatment (TABLE-2).

Pauline Joseph et al observed that, Time to culture conversion was 2 months or less for 31 (82%) patients. By 6 months, 35 (92%) patients had culture converted in a study conducted in Tamilnadu[14.]

V K Arora et al observed that, Out of the 66 patients included for analysis, 53(80.9%) patients achieved sputum culture conversion within nine months. Notably, among these 53 patients, 77.4% patients became culture-negative within three months and 92.5% became culture-negative within six months of treatment. Another four (6.1%) patients remained culture-positive even after receiving treatment for more than nine months[10].

Holtz PH et al observed that, under programme conditions in Latvia, most patients with MDRTB achieved sputum culture conversion within 12 weeks of starting treatment. Chest radiography and sputum culture drug

susceptibility testing can assist physicians in predicting which patients will convert more slowly[18].

Literature review shows that, culture conversion results are similar to our study that most of the culture conversion occurs within 12 weeks of initiating treatment.

In our study, Adherence level was good since defaulter rate was 3%.Among that 3 patients 1 patient has been traced and counselled and has been reregistered and started on DOTS PLUS therapy.1 patient has gone for native medicine treatment.

Arora et al observed defaulter rate of about 17.9% which is quiet high[10]. Similarly Pauline et al observed 13% defaulter rate[14]. Kwonjune J Seung et al observed that only one patient had defaulted in a study conducted across southern Africa where there is high HIV prevalence[19]. So, reviewing the studies shows that defaulter rate is low in our study which is very good.

Adherence to treatment was attained by strong health education to the patient and their family members prior to starting treatment and at periodic intervals, decentralized DOT supplemented with rigorous supervision by experienced health care staff, intense monitoring, prompt identification and management of adverse drug reactions, and involvement of community and family in providing DOT[14].

In our study, 15 patients have died within one year of starting MDR-TB treatment which should be evaluated carefully.

According to the Global outcome report on MDR-TB, death rate is 8% for new cases and 13% for previously treated cases[2]. Compared to new cases mortality is high in previously treated cases.

Study by V.K Arora et al observed 14.3% death rate[10], while Pauline et al showed 8% death rate[14.] Kwonjune J Seung et al observed 29% death rate, but in this study HIV coinfection was very high (74%)[19].

The cause for high death rate in our study should be evaluated and carefully followed up.

In our study, serious adverse events requiring stoppage of drugs for patients who has been started on DOTS plus is nil. Except for minor reactions which necessitated symptomatic treatment, major reactions are nil.

Reviewing literatue, V.K Arora et al observed 15.1% adverse reactions which required drug modification[10].

Pauline et al observed 58% severe adverse reactions[14] which required drug modification.

Reported minor events in our study group were nausea, vomiting, giddiness which responded to symptomatic treatment.

Our findings are similar to the results across the globe, observed in a Meta analysis which states that, Data on adverse events collected from five DOTS-Plus sites in Estonia, Latvia, Peru (Lima), the Philippines (Manila) and the Russian Federation (Tomsk Oblast) shows that among 818 patients enrolled on MDR-TB treatment only 2% of patients stopped treatment. The study shows that adverse events are manageable in the treatment of MDR-TB in resource-limited settings provided that standard management strategies are applied[20].

In our study group, 18 patients were Culture positive at the end of one year (TABLE & CHART-1).

V K Arora et al observed, Fifty-two patients enrolled upto December 2004 who had completed more than one-year treatment, for interim treatment outcome. Thirteen patients required intensive phase of more than six months (mean duration of 7.4 months). Thirty-six (69.2%) were likely to have been cured (clinically improving and sputum culture continued to be negative at one year), six (11.5%) died, six (11.5%) defaulted, and four (7.7%) were likely to have failed treatment (sputum culture positive even after 12 months)[10].

13% failure rate has been observed in a study conducted by Pauline Joseph[14].But this study comprises only 38 patients which is a limiting factor.

So cause for this failure should be evaluated and followed up carefully.

Further factors associated with death and culture positivity were analysed:

20% patients were diabetics among the 100 MDR-TB patients (CHART-2). Only 4(26%) were diabetic among who died.Infact only one (5%) is diabetic in culture positive patients. (TABLE-3&CHART-9).

Similar study in Tamilnadu during 2006-07 showed that off 38 MDR-TB patients, 12(31.5%) were diabetics[14].But this study does not analyse whether the patients who failed treatment and died during treatment are diabetics which is a limiting factor.

A study conducted at Govt.Hospital of Thoracic Medicine, Tambaram has showed that T2DM was significantly associated ($p<0.001$) with male gender (odds ratio 2.976), Middle aged (0.701 and 95% CI- .238-2.068) and Elderly aged (Odds ratio 1.0) groups. Younger age, history of smoking or alcohol use, HIV infection, urban or rural locality was significantly associated with no history of T2DM[21].

In our study, diabetes does not have significant impact on outcome of patients with MDR-TB.

HIV and MDR-TB Coinfection:

In our study, only 2 out of 100 MDR-TB patients had HIV coinfection (CHART-3).Among the two, one has died. The association between HIV and MDR-TB is very low in our study.

The 4th report on anti-tuberculosis drug resistance reported a significant association between HIV-positive status and MDR-TB in two settings: Latvia and Donetsk Oblast of Ukraine[2, 22].

Although there appears to be an association between drug-resistant TB and HIV infection in some Eastern European countries, the data are still limited to be able to determine whether there is an overlap between the MDR-TB and HIV epidemics worldwide[2].

Pre-treatment Weight among MDR-TB patients:

In our study, 93% of patients who died and 83% patients who were culture positive at the end of 1 year belong to < 45 kg weight band compared to only 43% in culture negative group (TABLE-4&CHART-10).

Pauline et al observed 52% of MDR-TB patients are in <45kg band whereas 47% of patients belong to >45 kg weight band[14].But this study does not analyse whether there is any association between low body weight and mortality and culture positivity.

Mortality and culture positivity is high in patients who are <45 kgs in our study. Whether there is any association between low body weight and outcome of MDR-TB has to analysed and these patients should be monitored carefully.

H,R,S,E resistance :

Resistance to all H, R, S, E drugs has been observed in 53% of died and culture positive patients. It is seen in 43% of culture negative patients (TABLE-3&CHART-9).In our study ,resistance to all four first line drugs does not have any significant impact on outcome of MDR-TB patients.

Socio-demographic profile of 100 MDR-TB patients:

In our study, 82 patients were males and remaining 18 were females (CHART-4). Similar study in Tamilnadu in 2006-07 observed 65% male patients and 35% female patients[14].

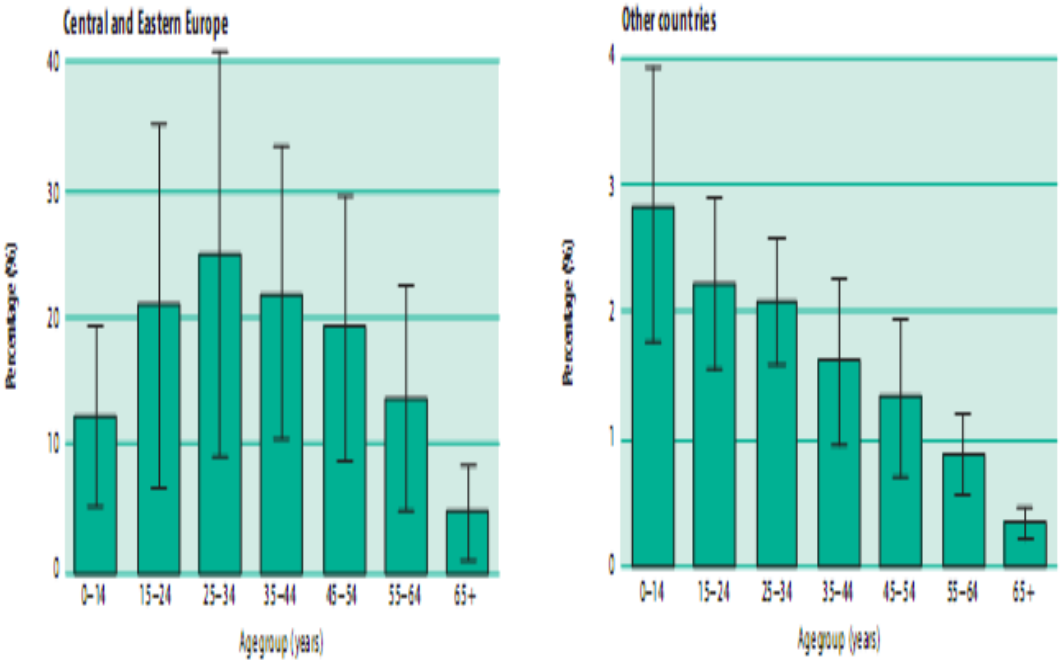
Surprisingly V K Arora observed 54% male patients and 46% female patients in his study[10].compared to other studies female ratio is high in this V K Arora study.

WHO global report states that, while males predominate among TB cases in most countries, this analysis suggests that the overall risk of harbouring MDR-TB strains is not influenced by sex[2]. Overall, combining data from these countries and territories (121 965; 58% males), and using the robust

standard errors approach, the odds ratio of harbouring MDR-TB strains for female TB cases compared with male TB cases was 1.1 (95% CI: 0.9–1.4), showing no overall association between MDR-TB and the sex of the patient[2].

In our study among 100 patients,38 patients belong to 15-34 yrs age group.47 were in 35-54 age group and 15 patients were in >55 yrs age group. Most of patients are in the <55 yrs group.

Percentage of MDR-TB cases by age group among all TB cases



Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response. WHO/HTM/TB/2010.3.

In our study, about 40 patients were smokers and 29 patients were alcoholic. But it does not have any impact on outcome of MDR-TB.

Difficulties in MDR-TB treatment programme:

Operational constraints to establish MDR-TB treatment programmes include setting up proper linkages of peripheral DOT centres with central hospitals for referral/admission; problems in enrolling patients due to work compulsions and inability to comply with daily DOT for two years; lack of ready access to specialised laboratory facilities; arranging daily DOT therapy for two long years, especially on Sundays and other holidays; managing severe adverse drug reactions in field conditions. An MDR-TB treatment trial in Rwanda found that nearly 50% of eligible patients died or were lost to follow-up while awaiting DST results from a distant reference laboratory[23].

Arranging proper training to medical, laboratory and non-medical workers for DOTS-Plus programmes is another operational constraint. Involvement of non-governmental organisation (NGOs) or local private practitioners proved to be of great help for some of these issues[10].

It has been acknowledged that good treatment is a pre-requisite to the prevention of emergence of resistance.RNTCP recognises that implementation of a good quality DOTS programme is the first priority for TB control in the country. Prevention of emergence of MDR-TB in the community is more imperative rather than its treatment[1].

Although the number of patients is 100, the early results have shown that use of carefully designed standardised treatment regimens with daily DOT for full duration, well-established NTP supported by highly motivated personnel and good linkage of peripheral and referral central hospital, can provide satisfactory results and can be implemented as part of a successful DOTS programme.

From this study, it appears feasible to treat MDR-TB patients effectively in India on the predominantly ambulatory RNTCP standardized regimen.

This study has given a broader view of patients who were started on DOTS PLUS therapy in Tamilnadu at the end of 1 year. Further the complexity of disease and treatment and development of XDR-TB among treatment failures are important issues to be addressed and should be carefully followed up.

Conclusion

CONCLUSION

Among 100 MDR-TB patients who were started on DOTS PLUS treatment in Tamilnadu, at the end of one year:

* High mortality and culture positivity at the end of one year are found in patients who were <45 kgs.

  Factors like Diabetes, Résistance to all first line drugs, Tobacco and Alcohol use and HIV does not have significant impact on outcome at the end of 1 year.

  Major adverse events were rare and Adherence to treatment is good.

* So it is very much essential to arrest the spread of resistant strains and to reduce the emergence of XDR-TB and help to decrease economic burden to the country in an indirect way. Timely identification of MDR-TB cases and adequately administered Category IV regimens are essential to stop primary transmission. DOTS/DOTS-Plus integration works synergistically to shut down all the potential sources of TB transmission.

Global target -2015:

While information available is growing and more and more countries are taking measures to combat MDR-TB, urgent investments in infrastructure, diagnostics, and provision of care are essential if the target established for 2015 – the diagnosis and treatment of 80% of the estimated MDR/XDR-TB cases – is to be reached.

Bibliography

BIBILIOGRAPHY

1. RNTCP DOTS PLUS GUIDELINES; www.tbcindia.org.

2. Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 Global Report on Surveillance and Response

3. B Mahadev, P Kumar, SP Agarwal, LS Chauhan, N Srikantaramu Surveillance of drug resistance to anti-tuberculosis drugs in districts of Hoogli in West Bengal and Mayurbhanj in Orissa. *Indian J of Tuberc 2005: 52(1); 5-10.*

4. CN.Paramasivan, C.Venkatraman, V. Chandrasekaran, S Bhat, PR Narayanan. Surveillance of drug resistance in tuberculosis in two districts of South India.Int J of TUBERC Lung Dis 2002:6(6) ;479-484.

5. Programmatic management of drug resistant TB (PMDT); www.tbcindia.org.

6. Tuberculosis Research Centre, Indian Council of Medical Research, Chennai, India. Low rate of emergence of drug resistance in sputum positive patients treated with short course chemotherapy. *Int J Tuberc Lung Dis 2001:5(1); 40-45.*

7. Clin Infect Dis. (2008) 47 (4): 496-502.

8. Lancet. 2005 Jan 22-28;365(9456):318-26.Clinical outcome of individualised treatment of multidrug-resistant tuberculosis in Latvia: a retrospective cohort study. Leimane V, Riekstina V, Holtz TH, Zarovska E, Skripconoka V, Thorpe LE, Laserson KF, Wells CD.

9. Int J Tuberc Lung Dis. 2008 Oct;12(10):1182-9.Treatment outcome and follow-up of multidrug-resistant tuberculosis patients, West Coast/Winelands, South Africa, 1992-2002.Shean KP, Willcox PA, Siwendu SN, Laserson KF, Gross L, Kammerer S, Wells CD, Holtz TH.

10. DOTS-Plus for Patients with Multidrug resistantTuberculosis in India: Early Results After Three Years .V.K. Arora, R. Sarin, R. Singla, U.K. Khalid, K. Mathuria, Neeta Singla and V.P. Myneedu

11. MARIE FLAMENT-SAILLOUR, JÉRÔME ROBERT Am. J. Respir. Crit. Care Med., Volume 160, Number 2, and August 1999

12. Lancet Infect Dis. 2009 Mar;9(3):153-61.Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis.Orenstein EW, Basu S, Shah NS, Andrews JR, Friedland GH, Moll AP, Gandhi NR, Galvani AP

13. Risk factors associated with default from multidrug-resistant tuberculosis treatment, South Africa, 1999-2001.Holtz TH, Lancaster J, Laserson KF, Wells CD, Thorpe L, Weyer K. Int J Tuberc Lung Dis. 2006 Jun; 10 (6) : 649-55.

14. Outcome of standardized treatment for patients with MDR-TB from Tamil Nadu, India.Indian J Med Res 133, May 2011, pp 529-534.

15. Singla R, Sarin R, Khalid UK, Mathuria K, Singla N, JaiswalA, et al. Seven-year DOTS-Plus pilot experience in India:Results, constraints and issues. Int J Tuberc Lung Dis 2009; 13 : 976-81.

16. Malla P, Kanitz EE, Akthar M, Falzon D, Feldmann K, Gunneberg C, et al. Ambulatory-based standardised therapy for multi-drug resistant tuberculosis: experience from Nepal, 2005-2006. PLoS One 2009; 4 : 08313.

17. Suarez PG, Floyd K, Portocarrero J, Alarcón E, Rapiti E, Ramos G, et al. Feasibility and cost-effectiveness of standardized second-line drug treatment for chronic tuberculosis patients: a national cohort study in Peru. Lancet 2002; 359 : 1980-9.

18. Holtz TH, Sternberg M, Kammerer S, et al. Time to sputum culture conversion in multidrug-resistant tuberculosis: predictors and relationship to treatment outcome. Ann Intern Med 2006; 144: 650–659

19. Early Outcomes of MDR-TB Treatment in a High HIV-Prevalence Setting in Southern Africa Kwonjune J. Seung[1*], David B. Omatayo[2], Salmaan Keshavjee[1], Jennifer J. Furin[1], Paul E. Farmer[1], Hind Satti[2]**.1** Division of Global Health Equity, Brigham and Women's Hospital,

Boston, Massachusetts, United States of America, **2** Partners In Health, Lesotho, Maseru, Lesotho.

20. Int J Tuberc Lung Dis. 2004 Nov;8(11):1382-4.Adverse events in the treatment of multidrug-resistant tuberculosis: results from the DOTS-Plus initiative.Nathanson E, Gupta R, Huamani P, Leimane V, Pasechnikov AD, Tupasi TE, Vink K, Jaramillo E, Espinal MA.

21. Diabetes Mellitus and Multi Drug Resistant Tuberculosis (MDR-TB)- A Tamilnadu experience. Velkumar G, Valan A.S, Mahilmaran A, Krishnarajasekhar O.R, Chandrasekar C. Government Hospital of Thoracic Medicine (GHTM).

22. Anti-tuberculosis drug resistance in the world: fourth global report (the World Health Organization/International Union against Tuberculosis and Lung Disease (WHO/UNION) Global Project on Anti-Tuberculosis Drug Resistance Surveillance 2002–2007). Geneva, World Health Organization, 2008 (WHO/HTM/TB.2008.394)

23. Muhlberger F, Nturanye F, Nsabimana J, Portaels F.Ofloxacin-cycloserine-prothionamide-INH combinationagainst treatment refractory lung tuberculosis. Pneumologie1995; 49: 72-6.

Proforma

PROFORMA

Name : Age: Gender:

Occupation :

Address :

Phone No :

Height/Weight :

Smoking : Yes / No

Brand/quantity/Duration

If stopped when?

Alcohol use : Yes / No

Brand/quantity/Duration

If stopped when?

Tobacco use : Chew/Snuff No of times/day

COMORBID CONDITIONS:

Pregnancy : Yes/No

Peptic ulcer : Yes/No

Bronchial Asthma : Yes/No

Hypertension : Yes/No

Diabetes mellitus : Yes/No

SYMPTOMS

Cough :

Fever :

Sputum :

Chestpain :

Haemoptysis :

Wheeze :

Contact history of Tuberculosis : yes/no

Previous history of Tuberculosis treatment:

If yes, Number of times of treatment,

Duration of treatment,

Regular /irregular

GENERAL EXAMINATION : BMI

Anaemia

Lymphadenopathy

Jaundice

Spine

Pedal edema

VITALS:

PR: BP:

RR: Temp:

EXAMINATION OF RESPIRATORY SYSTEM:

Inspection :

Palpation :

Percussion :

Auscultation :

PER ABDOMEN :

CARDIOVASCULAR SYSTEM :

CENTRAL NERVOUS SYSTEM :

INVESTIGATIONS:

Hemoglobin :

WBC Count :

Chest X-Ray :

MANTOUX :

SPUTUM for AFB :

CULTURE AND SENSITIVITY FOR AFB:

OTHER INVESTIGATIONS:

FINAL DIAGNOSIS:

ANNEXURE – II

CONSENT FORM

I Mr / Mrs / Miss / _____ have understood the procedure read by the Doctors. I in my whole conscious awareness give consent for the procedure. I understand that the procedure is done in good faith for the best therapeutic results possible. I fully understand the consequences of the procedure. I can resign from the study at any point of time.

Signature

Name :

Date and Time

Signature of Research